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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,374	05/21/2001	Ryuichi Morishita	Q64360	8301

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EXAMINER
CHEN, LIPING

ART UNIT	PAPER NUMBER
1632	4

DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,374	MORISHITA ET AL.	
	Examiner	Art Unit	
	Liping Chen	1632	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the claims

Claims 1-25 are pending and examined in this office action on the merits.

Priority

This application is filed on 05/21/2001,

which is a 371 of PCT/JP00/06347, filed 09/18/2000.

Foreign priority is claimed for JAPAN 11-267024, filed on 09/21/1999, and

JAPAN 2000-241205, filed on 08/09/2000.

Objection

The disclosure is objected to because of the following informalities:

Claim 2, states "cerebral infarction" twice. It is suggested to delete one.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 21-25 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for

example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21-25 provide for the use of HGF gene and/or VEGF gene in the manufacture of a therapeutic or preventive agent, but, since the claims do not set forth any steps involved in the methods/processes, it is unclear what methods/processes applicant are intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Claims 21-25 are treated as method claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to a therapeutic or preventive method for cerebrovascular disorders comprising introducing HGF gene and/or VEGF gene ino humans for different purposes, such as: preventing reduced blood flow (claim 3 and 14), promoting cerebral angiogenesis (claims 4 and 15), suppressing neuronal death (claims 5, 6 and 16), suppression apoptosis of nerve cells (claims 7 and 17), and treating or preventing other cerebrovascular disorders such as cerebral infarction, cerebral thrombosis, cerebral embolism, stroke, cerebral bleeding, moyamoya disease, cerebrovascular dementia, Alzheimer's dementia, and sequelae of cerebral bleeding (Claim 2).

However, the specification only provides the data of increasing reduced cerebral blood flow (specification, page 36, Example 4, Fig. 7) or preventing the reduction of cerebral blood flow (specification, page 37, Example 4, Fig. 8) as a result of the obstruction of the bilateral carotid arteries by injection of HVJ-liposome complex containing HGF or VEGF gene into the subarachnoid space of rats (300-400 g), and the data of suppressing the delayed neuronal death in the hippocampus CA-1 region as a result of ischemic stimulation of the bilateral carotid

arteries by injection of HVJ-liposome complex containing HGF or VEGF gene into the subarachnoid space of gerbils (50-70 g, specification, page 37-40, Example 5, and Fig. 11-13), there is no evidence the same therapeutic effect can be obtained from different animal or from a human. As regarding to animal models, Orkin et al. (Report for The Third Meeting of The NIH Investment in Research on Gene Therapy, August, 1995) states that "animal models are not satisfactory for studying many important human disorders, including cystic fibrosis, various cancers, and AIDS. Therefore, human studies are necessary to develop effective treatments for these and many other diseases" (Orkin, page 14, forth parag.). Moreover, Alonso de Lecinana et al. (Cerbrovasc Dis 11 suppl 1 : 20-30, 2001) teach that the development of ecperimental models of focal cereb ral ischemia has allowed for a better knowledge of its pathophysiology and for testing therapeutic strategies. However, most neuroprotective substances giving favorable results in these models have later not been shown to be clinically effective. The lack of agreement between the experimental studies and the clinical practice can be explained by reasons, such as the methods of the experimental model itself, by pathophysiological differences between experimental animals and man, and even by the fact that the substances tested have different pharmacological properties in the different species (Alonso de Lecinana, Abstract). In the instant case, the male Sprague Dawley rats and male Mongolia gerbils used is not proven to faithfully mimic the relevant human conditions. Further, the specification only provide an expression of c-Met, HGF

receptor, in the CA-1 region, it is not correlated with HGF are the key element in all cerebrovascular disorders. Furthermore, the only expression vector used in the instant invention is in the HVJ-liposome form and only transgene delivery is by administered into the subarachnoid space. There is no guidance as any other vectors can be used by any other administering method for any other cerebrovascular disorders, no guidance as to which cerebrovascular disorder should use HGF, to which should use VEGF or both, the claimed invention would have required one skilled in the art to engage in an undue amount of experimentation to achieve a therapeutic or preventive effect on a human for all cerebrovascular disorders encompassed the claims without a predictable degree of success.

The unpredictability in gene therapy has been widely recognized in the arts since the time of filing. Verma et al. (Nature, 389:239-242, 1997) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story. Verma et al. points out that the problems are the lack of efficient delivery systems, lack of sustained expression and host immune reactions (Verma, page 239, col. 1). Rozenberg et al. (S.T.P. Pharma Sciences 11:21-30, 2001) further explain that the choice of gene delivery vector is a key factor for the success of gene therapy application. It determines the efficiency of the gene packaging, unpackaging, expression and delivery to the site of interest (Rozenberg, Abstract). The requirements for a vector to have successful gene delivery include ability to produce high titer vector particles, ability for efficient transgene

expression for the desired duration, and low immunogenicity of the vector (Rozenberg, page 21, left col. sec. parag.). Nishikawa et al. (Human Gene therapy 12:867-870, 2001) further teach that the physicochemical properties of a DNA-vector complex will affect its passage through capillaried, extravasation, capture by the mononuclear phagocytes, and uptake by target cells. Interaction with blood components would alter these biodistribution. Since the complex is routed mainly to endosomes/lysosomes after its cellular uptake, it should be released into the cytoplasm and delivered to the nucleus. A carrier having the capacity to buffer the pH drop in late endosomes is also effective in releasing DNA into the cytoplasm, by destabilizing the endosome membrane (Nishikawa, page 862, col. 1 first full parag.). Balicki (Medicine 81:69-86, 2002) compares several vectors, such as Retrovirus, Adenovirus, Lentivirus, Adno-Associated Virus, Herpes Simplex Virus in different generation as well as liposome, protein/peptide and naked DNA, by means of cell target, chromosomal integration and immunogenicity (Balicki, page 70, Table 1) and teaches that the most common and useful strategy is to deliver the gene of interest to the nucleus and points out the extracellular barriers for such delivery include degradative enzymes (Balicki, page 70, left col. first parag.). With regard to gene therapy in brain, Castro et al. (Histol Histopathol. 16:1225-1238, 2001) teach that the brain offers a particular challenge for gene delivery to its constituent cells: it is encased by the skull, separated from the general circulation by the blood brain barrier, and made up of mostly non-dividing cells. The skull limits direct injection of

vectors into the brain, the blood brain barrier inhibits the easy entry of vectors injected into the bloodstream, and post mitotic target cells restrict what type of vector can be used to deliver genes to the brain (Castro, Abstract) and that the main challenges to neurological gene therapy are the inflammatory and immunogenic potential of the vectors currently available, the complexities in delivering genes to normal brain cells and achieving very long term and widespread distribution of transgene expression with no adverse effects (Castro, page 1234, first parag.). Taken together, the art teaches the fate of gene delivery is determined by vector used, gene encoded, protein produced, and cells targeted, these factors influence the fate of a transgene dramatically. Although the specification provides viral vectors for *in vivo* or *ex vivo* transgene delivery (specification, page 23, line 20-28), the specification does not provide any guidance as how to use any viral vector with any claimed gene for administering *in vivo* or *ex vivo* for any specific cerebrovascular disorder. It is noted that case law requires that the disclosure of an application shall inform those skilled in the art how to use applicants' alleged discovery, not how to find out, how to use it, for themselves (see In re Gardner et al. 166 USPQ 138 (CCPA 1970). The specification only teaches what is intended to be done, but does not actually teach how to do that which is intended.

As the specification fails to provide any evidence as introducing HGF gene and/or VEGF gene to a human with any cerebrovascular disorder to achieve a therapeutic effect, fails to teach the skilled artisan how to use any vector encoding

HGF gene and/or VEGF gene for further introducing into a human *in vivo* or *ex vivo* to achieve a therapeutic effect for claimed cerebrovascular disorders, the claimed methods are not enabled. Based upon the nature of the invention, the state of the prior art, the unpredictability in gene therapy, lack of direction or guidance as how to use any vector claimed to encode HGF gene and/or VEGF gene for different diseases, lack of direction as to which disease the HGF gene or VEGF should be used, to which disease both genes should be used together, lack of direction for the site of administering of transgene for each diseases, lack of direction as the dose of HGF or VEGF gene should be used for each cerebrovascular disorder, the claimed invention would have required one skilled in the art to engage in an undue amount of experimentation without a predictable degree of success to achieve any specific and the breath of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 1-9,11, 12 and 21-25 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Isner (WO 97/14307, published 04/24/1997).

Claims 1-9 and 11 are directed to a therapeutic or preventive agent comprising HGF gene and /or VEGF gene as an active ingredient; claim 12 is directed to a method of producing the agent by blending HGF gene and or VEGF gene with a pharmaceutically acceptable solvent; claims 21-25 are directed to a method of using HGF gene and/or VEGF gene in the manufacture of the therapeutic or preventive agent.

Isner teaches a pharmaceutical composition comprising a nucleic acid capable of expressing an angiogenic protein such as vascular endothelial growth factor (VEGF) or hepatocyte growth factor (HGF) (Isner, claims 1 and 3) for treating any ischemic tissue such as muscle, brain, kidney and lung (Isner, page 4, line 18-23), where the nucleic acid is formulated with a pharmaceutically acceptable carrier (Isner, page 11, line 21-22, pertaining to instant claim 12), which is obtained by using VEGF or HGF gene in the manufacture of the therapeutic agent (pertaining to instant claims 21-25). Thus, Isner clearly anticipates the claimed invention.

It is noted that the use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention

and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

Claims 13-17 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Isner (U.S. Patent 6,121,246, issued 09/19/2000).

Claims 13-17 are directed to a method for introducing HGF gene and/or VEGF gene into humans for different purpose such as: treating cerebrovascular disorders (claim 13) or reduced blood flow (claim 14), promoting cerebral angiiogenesis (claim 15), suppressing neuronal death (claim 16) or apoptosis of nerve cells (claim 17) in the brain.

Isner ('246) teaches a method of treating ischemic tissue such as muscle or brain ('246, col. 2, line 57) in a human ('246, claim 1) host by injection of the tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein ('246, col. 2, line 50-57), such as VEGF or HGF ('246, col. 3, line 9-18) in a pharmaceutically acceptable carrier ('246, col. 6, line 15-18) for the treatment of ischemia and thus diseases such as cerebrovascular ischemia ('246, col. 6, line 43-48). Thus, '246 clearly anticipates the claimed invention.

Further, the intended use of the compound does not constitute a step in the method as claimed. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure or

composition, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976); Kropa v. Robie , 88 USPQ 478, 481 (CCPA 1951).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Isner Isner (WO 97/14307, published 04/24/1997) in view of Morishita et al. (U.S. Patent 6,248,722 B1 issued 06/19/2001).

Claim 10 is directed to a therapeutic or preventive agent comprising HGF gene and /or VEGF gene as an active ingredient which is in the form of HVJ-liposome.

Isner teaches a pharmaceutical composition comprising a nucleic acid capable of expressing an angiogenic protein such as vascular endothelial growth factor (VEGF) or hepatocyte growth factor (HGF) (Isner, claims 1 and 3) for treating any ischemic tissue such as muscle, brain, kidney and lung (Isner, page 4, line 18-23),

'246 does not teach a therapeutic or preventive agent comprising HGF gene and/or VEGF gene in the form of HVJ-liposome.

However, Morishita et al.('722) teach to overcome the short half life of HGF in blood ('722, col. 1, line 46-48) by using HVJ-liposome-DNA form to achieve high level of expression.('722, col. 9, line43-61, and Figure 1) .

With the teaching of Isner of that a pharmaceutical composition comprising a nucleic acid capable of expressing an angiogenic protein such as vascular endothelial growth factor (VEGF) or hepatocyte growth factor (HGF) (Isner, claims 1 and 3) for treating any ischemic tissue, the teaching of '722 that to use HVJ-liposome for stabilize HGF, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the therapeutic agent of Isner by using preparing HGF gene and/or VEGF gene in the form of HVJ-liposome given results of '722 to increase the stability of transgene *in vivo* and achieve a higher level of HGF or VEGF expression *in vivo*.

Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (U.S. Patent 6,121,246, issued 09/19/2000) in view of Mann et al. (U.S. Patent 6,199,554, issued 03/13/2001).

Claims 19 and 20 are directed to a method for administering HGF gene and/or VEGF gene into humans together with the introduction of HGF protein and or/VEGF protein.

Isner ('246) teaches a method of treating ischemic tissue such as muscle or brain ('246, col. 2, line 57) in a human ('246, claim 1) host by injection of the tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein ('246, col. 2, line 50-57), such as VEGF or HGF ('246, col. 3, line 9-18) in a pharmaceutically acceptable carrier ('246, col. 6, line 15-18), for the treatment of ischemia and thus diseases such as cerebrovascular ischemia ('246, col. 6, line 43-48), where nucleic acid's encoding two or more different angiogenic proteins can be used separately or simultaneously in order to optimize the therapeutic outcome ('243, col. 3, line 7-8 and col. 6, line 4-7). '246 does not teach to administer VEGF or HGF protein together with introduction of HGF gene and/or VEGF gene.

However, Mann et al.('554) teach injecting into a tissue a revascularization-promoting molecule such as VEGF or HGF protein or nucleic acid molecule for revascularization ('554, col. 1, line 37-45 and col. 3, line 48-52). Mann et al. ('554) further teach that by combining "naked" plasmid injection with protein administration may allow a single infection of a gene encoding for a proangiogenic agent to produce sustained local protein production after which it could act in paracrine fashion and obviate the need for repeated administration of protein ('554, ocl. 7, line 47-56).

With the teaching of '246 that administering of nucleic acid encoding two or more different angiogenic proteins, such as VEGF and HGF, can be used separately of simultaneously to optimize the therapeutic outcome, the teaching of '554 that to

administering VEGF or HGF in protein form to obtaining a local protein concentration and combining with "naked" plasmid injection to limit the repeated protein administration, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of '246 by co-administering HGF protein and/or VEGF protein together with the introduction of HGF gene and/or VEGF gene so that required protein concentration can be reached immediately after protein administration, and the protein concentration level can be maintained by administering of gene which expressing the protein given results of '554 for enhancing the therapeutic outcome with less repeated administration.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liping Chen, whose telephone number is (703) 305-4842. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time). Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Pauline Farrier, Patent Analyst, at (703) 305-3550. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

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